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# BIYOMEDIKAL UYGULAMALAR IÇIN TITANYUM ALAŞIMLARININ EKLEMELI İMALATI

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**ÖZET:** Eklemeli imalat (AM) veya üç boyutlu baskının (3DP) önemli ilerleyişi, imalat sektöründe esneklik sağlayarak, müşteriye özel, karmaşık geometrilerin elde edilmesinin yolunu açmış ve çok sayıda araştırma-geliştirme çalışmasına hizmet ederek pek çok yeniliğe de öncü olmuştur. AM proseslerine endüstriyel ve akademik alanlardaki ilgi giderek artmaktadır. Son yirmi yılda, eklemeli imalat ile biyomalzeme üretimi önem kazanmış ve eklemeli imalat ile elde edilen implantlara olan talep de aşırı artmıştır. Eklemeli imalat ve biyomalzeme kombinasyonu, özellikle hastaya özgü klinik uygulamalara yönelik gelecek vaat etmektedir. Bu bağlamda, 3D basılabilir biyomalzemeler implantlar için uygun bir seçenek olmuştur. Biyouyumlu, çok yönlü ve uyarlanabilir, ilgili mekanik (dayanım ve rijitlik) ve biyolojik işlevselliklere, gözenekli yapıya, tasarım serbestliğine sahip olma, malzeme tasarrufu sağlama, yüksek doğruluk ile üretim, geometride tasarım gereksinimlerini gerçekleştirme özellikleri sayesinde eklemeli imalat implantlarının miktarı önemli ölçüde artış göstermiştir. İmplant biyomalzemeleri, istenilen bir işlevi elde etmek için yüksek yorulma, aşınma ve korozyon direnci, stabilite, osteogenez ve osseointegrasyon özelliklerinin yanı sıra uzun ömre sahip olmalıdır. Bu çalışma, en yaygın olarak kullanılan implant biyomalzemelerinden olan Ti ve Ti6Al4V alaşımlarının mekanik özellikleri, biyouyumlulukları ve bu biyomalzemelerin mevcut uygulamaları bakımından farklı eklemeli imalat çalışmalarını incelemektedir.

**Anahtar Kelimeler:** Biyomalzemeler, Eklemeli İmalat, İmplantlar, Titanyum, Titanyum Alaşımları.

# ADDITIVE MANUFACTURING OF TITANIUM ALLOYS FOR BIOMEDICAL APPLICATIONS

**ABSTRACT:** The significant progress of additive manufacturing (AM) or three-dimensional printing (3DP) has induced a revolution in the manufacturing sector providing high flexibility, the feasibility of complex geometries in customization at the consumer level, and also serving as an efficient tool for further research and development. AM processes are increasingly attracting many interests in industrial and academic fields. In the last two decades, biomaterial production with AM has gained significance, and the additively manufactured medical implant demand also has undergone explosive growth. AM and biomaterial combination are very promising, especially towards patient-specific clinical applications. In this context, 3D printable biomaterials are suitable candidates for implants and the amount of additively-manufactured implants is significantly increasing due to their unique properties which are biocompatible, versatile, and adaptable, have relevant mechanical (strength and stiffness) and biological functionalities, porous structure, design flexibility, provide material save, produce with good accuracy, fulfill design requirements in geometry. Implant biomaterials should have high fatigue, wear, corrosion resistance, stability, osteogenesis, and osseointegration properties as well as a long lifespan to achieve an intended function. This study overviews the different studies on AM of the most widely used implant biomaterials Ti and Ti6Al4V alloys, in terms of mechanical properties, biocompatibility, and current state of applications of these biomaterials.

**Keywords:** Additive Manufacturing, Biomaterials, Implants, Titanium, Titanium Alloys.

## 1. INTRODUCTION

In today's manufacturing industry, the increasing demand for more custom and high complexity components became a strong motive for the advancements in AM technologies. These technologies are becoming more popular over the recent decade and research is rapidly progressing in this field across both scientific and industrial sectors [1, 2]. In contrast to conventional processing methods, which are beginning from stock material, the basis of AM is to generate a part by adding material according to a computer-aided design (CAD) model. AM is an innovative, versatile, flexible manufacturing technology and identified by the American Society for Testing and Materials (ASTM) as "the process of joining materials to make objects directly from 3D model data, usually layer upon layer, as opposed to subtractive manufacturing methodologies, such as traditional machining" [3]. By achieving the complex parts economically, providing material savings, and allowing customization, AM has various applications in different sectors including aerospace, automotive, energy, construction, architecture, biomedical, electronics, and military [4-6].

AM's second largest industry is medical only after the automobile sector [7]. AM has a significant market share in the medical industry and outstanding potential for patient-specific parts. Small quantities of custom and complex components that satisfy the requirements of patients can be manufactured additively with relatively low costs as well as lead and manufacturing times. Recently, with the existing AM processes various applications of biomedical have been performed, such as artificial organs, surgical tools, hearing aids, implants, prostheses of joints (e.g. hip, knee), stents, bone grafting, diagnostic platforms, drug delivery systems (DDS) and soft tissues [8-16]. Researches intensified especially on additively manufactured custom implants that can be challenging to generate with conventional processes.

Biomaterials perform tissue and organ restoration via interacting with living systems and performing or supporting their functions to enhance the health and the life quality of patients. In recent years, additively manufactured biomaterials are very promising and gained importance in particular patient-specific medical products since AM is a specific system for design and material. Various medical implants from scanned image data can be produced with AM. Metals, ceramics, polymers, and composites are biomaterials of implants. Especially metals and alloys are widely preferred for additive manufactured implants as biomaterials due to their superior strength and toughness, such as Ti6Al4V, CP Ti, NiTi, CoCrMo alloy, SS, Mg, Zn [17-23].

AM applications in the medical industry, especially implants, and research on this topic are on the continuous increase. This paper focuses on the AM of titanium and its alloys for patient-specific implants. Followed by the introduction, the AM processes are summarized. Then, the property requirements and manufacturing of implants by AM, Ti, and its alloys, their AM, osseointegration are discussed in detail, respectively. We conclude with a summary. It is hoped that this study will be beneficial for understanding the current state of AM of Ti-based implants.

## 2. ADDITIVE MANUFACTURING PROCESSES

To express AM process, different definitions can also be used such as solid freeform fabrication, rapid manufacturing, layered manufacturing. Production is performed by material deposition in layers consecutively converting CAD files into the STL (Standard Triangulation/Tessellation Language) or VRML (Virtual Reality Modeling Language) formats that allow cutting the object into slices for manufacturing. Then, the path of the tool along the x and y directions is generated by an AM machine, and process parameters are determined before manufacturing. Each layer is cumulated upon the other, achieving a 3D object. AM technologies are categorized into seven classes by ASTM International standards which are material extrusion, powder bed fusion, direct energy deposition, material jetting, binder jetting, sheet lamination, and vat photopolymerization [24]. Table 1 summarizes these AM processes. Each AM process is different based on the material, energy source as well as technology. These techniques differ according to processed materials, material feedstock form, distribution of the source material (such as via powder bed or nozzle) and, applied heat sources (laser, electron beam, or arc) among others. Each AM method has specific applications based on its advantages.

**Table 1.** Additive manufacturing processes.

| ASTM Category | Techniques | Material | Feedstock form | Reference |
|---|---|---|---|---|
| **Material extrusion (ME)** | • Fused Deposition Modeling (FDM)<br>• Fused Filament Fabrication (FFF)<br>• Pneumatic Extrusion (PE)<br>• Syringe Extrusion(SE)<br>• Robocasting | Polymers, Metals, Ceramics, Composites | Filament | [25,26,29]<br>[26,29]<br>[28]<br>[28]<br>[29] |
| **Powder Bed Fusion (PBF)** | • Selective Laser Melting (SLM)<br>• Selective Laser Sintering (SLS)<br>• Direct Metal Laser Sintering (DMLS)<br>• Electron Beam Melting (EBM)<br>• Multi Jet Fusion(MJF) | Polymers, Metals, Composites, Ceramics | Particle/Powder | [29,30,31]<br>[29,32]<br>[29,33]<br>[29,34,35]<br>[29] |
| **Direct Energy Deposition (DED)** | • Laser Engineered Net Shaping (LENS)<br>• Laser Deposition Welding (LDW)<br>• Laser Cladding (LC)<br>• Cold Spray (CS)<br>• Laser Additive Manufacturing (LAM)<br>• Direct Metal Deposition (DMD)<br>• Wire Arc AM (WAAM) | Metals, Composites, Ceramics | Particle/Powder, Wire | [29,36]<br>[28]<br>[37]<br>[29]<br>[29]<br>[25,29,38]<br>[25,29] |
| **Material Jetting (MJ)** | • Drop on Demand (DOD)<br>• Poly Jet<br>• Multi-Jet Modeling (MJM)<br>• Nanoparticle Jetting (NPJ) | Polymers, Metals, Composites | Liquid | [26,29]<br>[25,29]<br>[27,29]<br>[26,29] |
| **Binder Jetting (BJ)** | • Ink-Jet 3DP (3DP) | Polymers, Metals, Ceramics, Glass | Particle/Powder | [28] |

| | | | | |
|---|---|---|---|---|
| **Sheet Lamination** | • Laminated Object Manufacturing (LOM)<br>• Ultrasonic AM (UAM)<br>• Ultrasonic Consolidation (UC) | Metals, Composites, Polymers | Sheet | [25,26,29]<br>[25,26,29]<br>[29] |
| **Vat Photopolymerization(VP)** | • Stereolithography (SLA/SL)<br>• Continuous Liquid Interface Production (CLIP)<br>• Digital Light Processing (DLP)<br>• Multiphoton Polymerization (MPP) | Polymers, Ceramics | Liquid | [26,29]<br>[28,29]<br>[26]<br>[27] |

## 3. PROPERTY REQUIREMENTS AND MANUFACTURING OF IMPLANTS

Especially during aging, elasticity loss of bones results in brittle deformation and fracture of the bone. This gains importance when there is direct contact between brittle bone and rigid implant materials. Temporary and permanent implants are used to treat these damages and disorders of skeletal resulting from trauma or diseases (e.g. tumors, osteoporosis) through the reconstruction of bone.

Implants should enhance the life quality of patients by extending the functionality of essential body systems beyond their supposed lifespans, meeting the long-felt need, repairing or supporting damaged tissue function, and satisfying the patient's esthetic and functional requirements. Implant material should not bring about any health hazard, so it should have biocompatibility to patients during their lifespan without failure. Microstructural, biological, and mechanical properties of the material have an impact on the implant's long-term performance. For an implant, there are some important factors including mechanical properties (high strength, toughness, wear, and corrosion resistance, appropriate stiffness, low elastic modulus in the range of host bone), porosity and roughness for attachment, growth, and proliferation of cells, biocompatibility, bioactivity, osteogenesis, and nontoxicity. Bone and implant's elastic modulus should be similar to prevent the stress-shielding phenomenon, which occurs because of the implant's larger stiffness in comparison with the adjacent bone's stiffness. This leads to periprosthetic bone resorption by the reason of decreased loading at the peri-implant bone. The mismatch of mechanical characteristics between the adjacent bones and the implant causes a load distribution incorrectly [39-42]. Also, to provide implant stability that can be identified as clinical immobility, biomaterial should have similar mechanical properties as bone [43]. Moreover, suitable resilience degree and damping features –super-elasticity- of the implant materials prevent failure and fracture possibility of bone after implantation [44]. The accurate shape and geometry of biomedical implants are needed to perform their functions properly [45, 46]. In contrast to conventional methods that are not suitable for meeting these requirements, AM optimizes them simultaneously with novel designs, increases implant performance, overtakes traditional techniques to design and manufacture implants in lesser time with better specifications, high accuracy at lower cost, and provides implants with high dimensional stability and near net shapes [47, 48]. AM supports the conversion of the custom implant original design to the physical model.

Patient-specific implants (PSIs), which are also stated as custom, provide various advantages: They are processed to provide precisely match the margins of the bony defect that enhances the fixation stability. Thus, the mismatch risk is minimized. PSIs might provide outstanding cosmesis restoration that is crucial in craniofacial operation. Also, they are obtained pre-operatively with a reference to a patient's craniofacial defect's 1:1 scale model and avoid intraoperative manufacturing processes that might enhance the efficiency of the surgical process as well as patient effects [49].

AM processes provide PSIs according to the individual patient data [50]. They can also control the morphology of both external and internal simply along with the production of the implant. Adaptation of external morphology to the patient-specific dimensions of defect is possible. For this, 3D data that changes from patient to patient is required. However, optimization is required to define the internal morphology of implants and cannot be fully automated, yet. Before CAD modeling; Magnetic Resonances Imaging (MRI), Computerized Tomography (CT), Coordinate Measuring Machine (CMM), laser scanning, positron emission tomography, ultrasound scanning technologies are employed to generate accurate model data of patients [51]. These scans are suitable for image acquisition and this step is very important to capture patient's accurate data in the design process. MRI provides a powerful non-ionizing method to determine anatomical structures, irregularities as well as the abnormal and normal tissue information, emphasizes post-operative complications, and is employed with the CT data for imaging sequences with higher resolution. CT provides bone's detailed information since high geometric accuracy and spatial resolution are obtained. CT scan increases the patient's comfort with the property of high scanning speed. In the segmentation step, various software programs such as OsiriX Imaging Software, 3D doctor, 3D Slicer, InVesalius, Magics, Mimics, Simpleware are employed to transform captured data to the 3D virtual model [52]. Scanning image data is converted to 3D CAD models and simulation is performed by software programs and Digital Imaging and Communications in Medicine (DICOM) directory [53]. The images are collected and stored in DICOM file format to make a custom implant. A material is determined for the image of the patient, which represents the interest regions, so the reconstructed virtual model is obtained. The digital CAD model is converted to STL or VRML formats. To generate these formats of implants, a standardized procedure is followed [54]. For example, to create the STL model, the point cloud data can be processed in Geomagic Design X 16.11 (3D Systems, Inc., USA) employing an automated triangulation algorithm [55]. To assess the dimensional accuracy, which is very significant for additively manufactured Ti PSIs in mandibular reconstruction and can be determined by a micrometer, between the scan data and CAD model, accuracy analysis can be carried out [56]. After this, depending on the various factors including the layer thickness, manufacturing speed, temperature, orientation, raster angle, hatching distance, contours, and corresponding parameters; the requirements of implants can be determined based on the literature or experiences, and then AM is finished. AM process of implants has been completed at eight major steps as shown in Fig.1. These steps can be generalized under acquisition of image, segmentation, CAD, AM, and clinical application. As designs of custom implants are performed for an individual patient, finite element analysis (FEA) is needed to forecast the stresses on the implant and adjacent bone. To select the implant (custom or generic), FEA's stress analysis results can be utilized [57, 58].

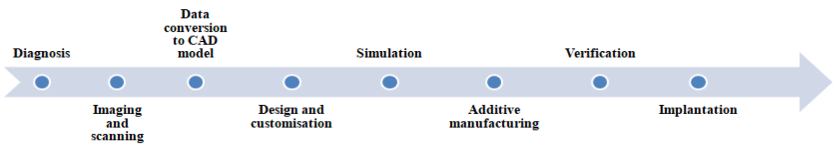



**Fig. 1.** Steps of additive manufacturing process for implants.

## 4. TITANIUM AND TITANIUM-BASED ALLOYS

Titanium (Ti) and alloys are the most commonly used materials in the medical industry as implant biomaterials due to their great biocompatibility, osseointegration, and superior properties that are presented in Table 2 [59]. Ti alloys have low elasticity modulus, higher strength to weight ratio, and perform better biocompatibility due to the excellent corrosion resistance than other metal implant materials as SS and Co-based alloys [60, 61]. These implants can provide load-bearing, stability, and mechanical stimuli transfer to bones, promote bone growth and reduce the loosening risk. Ti alloys exhibit good fatigue strength and toughness, but high friction coefficient, low hardness, and poor wear resistance. These alloys are inconvenient for applications that required high wear resistance [62, 63]. To improve Ti alloys' wear resistance and hardness, surface modification techniques can be used. Fatigue strength is the maximum stress, which a material can resist for a specified cycle number without fracture [64]. Corrosion resistance is the feature, which identifies the deformation of material characteristics resulting from the reaction with surroundings [65]. Wear resistance is the parameter that specifies the service life of the friction materials and depends on the manufacturing technique and ingredients [66].

**Table 2.** Properties of Ti, Ti6Al4V, and bone [67-72].

| **Property** | **CP Ti** | **CP Ti (SLM)** | **Ti6Al4V** | **Ti6Al4V (For EBM and SLM)** | **Bone**<br><br>**Cortical y60-69**<br><br>**(Respectively for femur and tibia)** | **Bone**<br><br>**Cancellous respectively tibia (y60-83) and femur (y58-83)** |
|---|---|---|---|---|---|---|
| Young's modulus (GPa) | 106 | 112 | 113 | 0.57, 3.5 | 17, 20 | 0.61, 0.39 |
| Tensile strength (MPa) | 240-550 (according to grades) | 703 | 960 | - | 129, 147 | - |
| Yield strength (MPa) | 170-480 (according to grades) | 620 | 805 | 7.28, 125 | 112, 124 | - |
| Biocompatibility | Yes | | Yes | | | |
| Degradation | No | | No | | | |
| Radiology (X-Ray, CT, MRI) | Visible | | Visible | | | |

Al, V, Ni, Fe, Nb, Zr, Ta, Mo are alloying elements of Ti used in medical products [73]. Ti, Nb, Zr, Ta, and Mo elements have good corrosion resistance in simulated human fluids, and therefore a highly protective surface film on the alloys can occur. By altering the ratio of the alloys' constituent elements, the mechanical properties and morphology of alloys can be regulated [74]. Ti6Al4V (Ti64) is tough, lightweight, biocompatible with the human body, suitable for bone growth, and corrosion-resistant as well as one of the most commonly used Ti alloys [75]. Ti alloy implants' 80% has this material [76]. Because of the properties of allotropy and the related microstructures' diversity that exist in Ti alloys, Ti is appropriate for AM processes. The densities of Ti and Ti64 are 4.5 and 4.41 g/cm$^3$, respectively [77, 78]. Ti64 is used as biomaterial of implants such as clavicular, mandibular, dental, knee, and hip [79]. Zr is used in Ti alloys to enhance their mechanical features. This element's biological behavior is similar to Ti, it has good biocompatibility and nontoxicity. Zr and Zr alloys are bioactive metallic biomaterials since they can generate an apatite layer like bone on their surfaces in the body. Furthermore, this element has a high fracture toughness, mechanical strength, and good corrosion resistance. Thus it can be used as a structural material for biological hard tissue replacements [80]. In vivo studies of Ti, Nb, and Ta presented good biocompatibility [81]. Nb, Ta, and Mo elements generally increase the chemical stability of the oxide film on the surface [82-84]. Additively manufactured Ti and its alloys used in the biomedical industry are given in Table 3.

**Table 3.** Additively manufactured Ti-based alloys for biomedical applications [12, 85, 86].

| Material | Applications |
|---|---|
| CP-Ti | Screw and abutment |
| Ti6Al4V | Artificial valve, stent, bone fixation |
| Ti-6Al-7Nb | Crown, knee joint, hip joint, femoral prosthesis stem |
| Ti-5Al-2.5Fe | Spinal implant, femoral prosthesis stem |
| Ti-15Zr-4Nb-2Ta-0.2Pd | Crown, bridge, denture, implant |
| Ti-29Nb-13Ta-4.6Zr | Crown, bridge, denture, implant |
| NiTi | Catheter, stent |

## 5. ADDITIVE MANUFACTURING OF TI-BASED IMPLANTS

Machining of Ti and its alloys is costly and the lead time of traditional processes for them is relatively long. In this context, AM provides an important cost-effective approach by fabricating parts with a high geometric degree of freedom with material saving and shorter time. Moreover, the property of allotropy and wide range of related microstructures in Ti alloys make Ti as well as its alloys ideal for AM processes.

The first clinically confirmed additively manufactured metal implant, which has a customized geometry and porous structure, in the world, was made by PBF of Ti alloys in Italy based on the patient acetabular cup [87]. PBF and DED are the most widely exploited AM techniques for implants of Ti and Ti64 such as dental implants manufacturing. In the study of Mangano et al., Ti dental implants obtained by DMLS, which is a PBF process, presented acceptable clinical results in short term [87]. PBF meets specific needs of metal implants including design flexibility without the requirement of rigid support, high dimensional accuracy, high performance [88-91]. Recently, SLM, EBM, LENS, and SLS are used to manufacture orthopedic and porous Ti-based implants with tailored properties that can emulate human bone [92-94]. Vandenbroucke et al. applied a digital methodology to make a custom model for high complexity dental prostheses that verify the economical potency of SLM for biomedical components [91]. Murr et al. have investigated the differences between Ti64 medical parts obtained by conventional manufacturing and SLM with EBM [92]. Traini et al. presented the effectiveness of SLS for dental implants [93]. Otawa et al. presented the dimensional accuracy of Ti specimens manufactured by SLM process. The results of this study pointed out the suitability of SLM to make custom Ti parts with different morphologies and high accuracy [94]. In Figure 2, ultimate tensile strength (UTS) and elongation values of Ti64 obtained with different AM processes are presented [95, 96]. According to ASTM, values of UTS and elongation of as-prepared Ti64 should be no lower than 860 MPa, and 10%, respectively. These two values are indicated with dotted lines in Fig. 2.

EBM enables both good fracture strength and ductility while meeting ASTM specifications. Ti64 alloy processed by SLM has the highest fracture strength among four AM technologies, however, its elongation is lower than 10%. The LENS process provides good strength, but the ductility of the alloy is not stable. To obtain good fracture strength and ductility, Ti64 alloy processed by SLS needs post-treatment such as a HIP (hot isostatic pressing) due to low density. These processes are suitable for AM especially for orthopedic and dental implants that should be compatible, rapid, and cost-effective. Ti implants with flexibility closer to the bone and different geometries can be developed.

After implant manufacture and in vitro study, biocompatibility test through in vivo analysis is carried out by placing implant inside an animal (such as sheep, rabbit, rat). Also, tests of biocompatible titanium alloys fabricated by SLM, EBM, and LENS can be found in the literature [11, 97-102]. Łyczkowska et al. used an approach to polish chemically the surfaces of Ti-6Al-7Nb scaffolds achieved by SLM for improving the quality of surfaces and eliminating powder particles inside the porous component [97]. Van Bael et al. examined the relationship between pore shape and size, porosity as well as permeability and mechanical characteristics with in vitro results of Ti64 scaffolds made by SLM [98]. Fukuda et al. evaluated the effectivity of interconnective pore size on the formation of bone and osteoconductivity in Ti implants obtained by SLM [99]. Wang et al. studied Nb quantity's impact on SLM manufactured Ti-Nb alloys' phase transformation, mechanical characteristics, microstructure as well as in-vitro apatite-formation ability [101]. Arabnejad et al. presented two different topologies, a visualization approach to investigate the relation of the limits of bone ingrowth needs and AM with the topology of the cell, pore quantity, and dimension. Also, they showed the bone ingrowth phenomenon into biomaterials having porosity and high strength in their study [102]. The literature review supports that additively manufactured implants are highly dimensionally stable and have near net shapes.

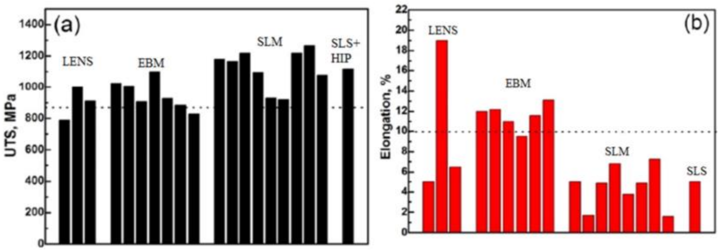


**Fig. 2.** a) UTS and b) Elongation of Ti64 processed by various AM techniques [96].

## 6. OSSEOINTEGRATION

Osseointegration implies the connection between tissue and implant and is especially significant to minimize as well as prevent implant failure because of inadequate integration of the implant to the bone. Osseointegration of Ti surface with bone can be improved with various approaches including enhancing osteoconduction, which defines directing the activation of bone formation on or at a determined surface, incorporating osteoinductive factor by applying growth factors, and micro-/nano-topological surface modification [103]. In this sense, porosity plays a key role, since it can provide necessary osseointegration for sufficient bone-implant fixation, cause better implant stability and enable bone in-growth to a porous surface, so implant life increases in vivo [104-106]. Porous components are suitable for orthopedic implants for improving osseointegration and reducing stress-shielding [107-109]. Implants should have a porosity value between the range of 50-70% for sufficient osseointegration. Metal implants should have more than 75% porosity to be highly porous [110]. Porosity increase can be achieved in AM processes. Porous Ti structures by processing LENS were achieved with up to

70% volume porosity [110, 111]. Krishna et al. demonstrated the effect of LENS process parameters on Ti implants' mechanical characteristics and porosity [111]. Xue et al. presented the capability of Ti samples fabricated by LENS to be utilized as a bone implant for load-bearing [112]. In the study of Murr et al., Ti64 implants samples with a porosity of 83% are manufactured with EBM [103]. In the studies, porous Ti-based implants enhanced osseointegration with bone tissues and porosity amount has a considerable effect on tissue in-growth [113-118]. Campoli et al. presented that SLM porous implants with multiple roots can have stronger bonding between the implant and bone. They investigated finite element models of porous Ti parts fabricated by SLM to evaluate the mechanical characteristics [119]. Attachment, the proliferation of cells, and thus osseointegration increases with surface micropores [120, 121]. In traumatology implants, Ti64 is the most commonly utilized since its properties of processability, high yield strength at room temperature. This alloy generates a $TiO_2$/OH film on the surface of the bone and activates cell adhesion after implantation, thus rapid osseointegration occurs [122]. Moreover, osseointegration can be improved due to the high permeability property of Ti implants [123, 124]. During implantation, as the surface of the implant contacts tissue firstly, the surface has a significant effect in the determination of the implantation success and implant performance. Osseointegration is enhanced with the roughness of the surface at the scales of micro as well as nano [125]. He et al. reported that bone apposition can be improved with roughness in $H_2O_2$/HCl heat-treated Ti surface [125]. Porosity and roughness provide effective and rapid osseointegration by helping new bone formation. Micro-porosity also improves osteogenesis, which defines bone formation and development process as well as osteoprogenitor cells' and extracellular matrix secretion's differentiation process [126, 127]. Some additively manufactured Ti implant samples with the main properties for osseointegration are given in Table 4 and Fig. 3 [128-131]. The osseointegration rate is affected by surface wettability that can be determined with the contact angle measurement [132]. If the contact angle is low, wettability is high, the surface is hydrophilic [133]. In contrast to hydrophobic surfaces, hydrophilic surfaces of implant cause improved early osseointegration [134, 135].

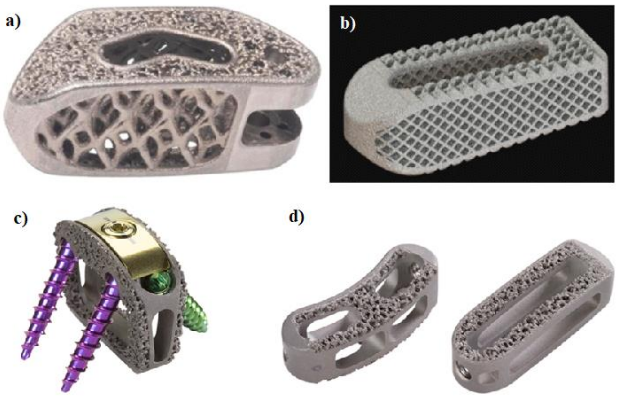



**Fig. 3.** a) Spine implant, b) Lumbar interbody, c) Cage, d) Transforaminal Lumbar Interbody Fusion (TLIF) System [128-131].

**Table 4.** Ti implants, their manufacturer, design, and properties [128].

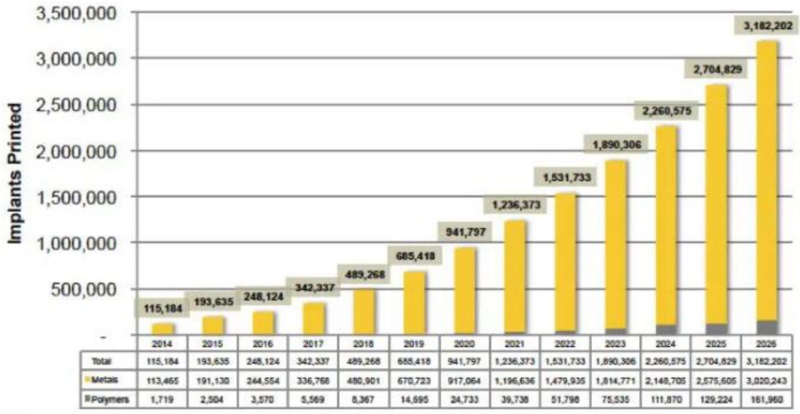
| Company | Implant/Design | Properties |
|---|---|---|
| NUVASIVE, INC | Spine implant / Modulus TLIF-A | Similar porosity with bone as well as endplate texture |
| SPINEART | Interbody implant/Juliet Ti | Porosity: 70%-75% Interconnected |

| | | |
|---|---|---|
| KYOCERA MEDICAL TECHNOLOGIES, INC | System of spinal cage /Tesera SA Cage System (with EBM process) | In layers, gradient of porosity: 57-72-91% Roughness of surface is at the scale of micro |
| KYOCERA MEDICAL TECHNOLOGIES, INC | Acetabular System/Tesera Trabecular Technology (with EBM process) | In layers, gradient of porosity: 57-72-91% Roughness of surface is at the scale of micro |
| OSSEUS | Interbody fusion devices/Aries$^{TM}$ (with EBM process) | Porosity: 80% |

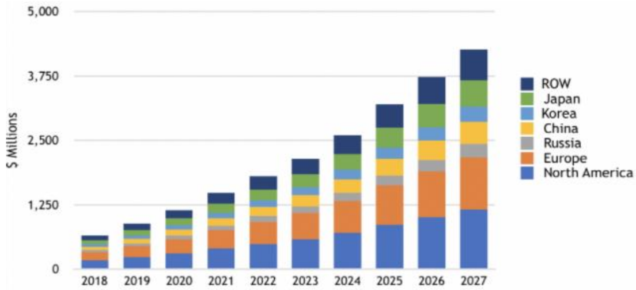
There are various methods to provide and improve contact formation between the bone and implant [136]. The surface of Ti which has a silica coating with porosity of nanoscale and nanoparticles of bioactive glass was produced in one study and obtained that this increases apatite and bone formation near-by implant 3 weeks later [137]. Another study has presented that as compared with other implant surfaces, surfaces with structure at nanoscale enhance osseointegration in Ti implants since verified through the improved contact between implant and bone as well as the growth of bone values. In addition, the surface oxide layer of Ti implants has a significant impact to enhance biocompatibility [138-140]. Different oxidation approaches including thermal oxidation, alkali treatment exist to enhance Ti implant osseointegration [141, 142]. Umehara et al. presented the suitability of alkali hydrothermal treatment to increase the stability of implants thanks to osseointegration [143]. Moreover, to improve osseointegration of Ti implants with porosity, bioactive and superelastic coatings can be applied as a significant tool. In a different study, Ti implants with $CaCO_3$ coatings were sandblasted as well as etched with acid and the observations were early bone ingrowth with the improvement of osseointegration. This was due to osteoblast response resulting from Ca ions mediated by the integrin [144]. To improve Ti osseointegration and biocompatibility, graphene coatings at the nanoscale are also used and important for defect reconstruction of bone [145]. Li et al. demonstrated that Ti alloy scaffolds' biocompatibility was improved with graphene coating [145]. Heat and alkali treatment, Na ions removal, hydroxyapatite (HA) coatings, and topography modifications, affects biofilm formation and cell attachment, can also improve osseointegration of Ti implants [146-148]. Micro-/nano-topography applied on Ti surface can affect surface hydrophilicity enhancing affinity to cells and proteins that present mechanical cues to cells, inducing osteogenic differentiation [149-153]. Acid/alkali etching and blasting are applied to generate micro-/nano-topography that are conventional surface treatments. Biologic activators' application and the chemical composition of the surface modification can directly affect cell differentiation and improve contact osteogenesis [71]. To create HA coatings on porous Ti-based parts, micro-arc oxidation, hydrothermal treatment, electrophoretic deposition, biomimetic coating approaches can be applied [154-159]. Also, $TiO_2$ development on the surface provides better osseointegration [17].

## 7. RECENT TRENDS AND FUTURE PERSPECTIVE

In 2020, the largest sector was medical implants with 32% of the total market share and it can be said that this position will remain the same in the upcoming years because of the increasing need and demand for implants. Medical AM's market value was 1.34 billion $ in 2020. Between 2021 and 2028, the compound annual growth rate is estimated as 21.8%. Market sizes are 1.61 billion $ and 6.44 billion $, respectively in 2021 and 2028 [160]. As AM is advantageous for custom implant production, the amount of implants obtained with AM tends to increase over the years as shown in Fig. 4 (a). According to this graph, it is obvious that additive manufactured metal implant (mostly Ti and Ti64 along with outstanding properties) amount will increase and mass-customization of metal implants will become widespread.




a)




b)

**Fig. 4.** a) Additive manufacturing timeline for implants, b) Income from additively manufactured medical parts by regions [161-162].

In Fig. 4 (b), additively manufactured medical components revenues from different regions are presented. There is high competition in this market. Most of the revenues are provided from North America and Europe. In 2020, the largest economic share for additive manufactured medical components belonged to North America with 35.5%.

## 8. CONCLUSION

AM is becoming more common with recent advancements in the medical field targeted to implants, across industry and academy. Implant design is getting more complicated day by day since the needs of patients differ and conventional methods are not appropriate for meeting these requirements. AM plays a key role in providing custom, precise and biocompatible implants based on patient data through scanning technologies, and additively manufactured implant demand has increased. These implants with the use of Ti-based biomaterials serve to support or perform the function of or replace damaged tissue. Mechanical features and biocompatibility of Ti make it suitable for implants as well as its suitability has been verified with literature and experimental studies. Here, we reviewed features that implants should have, Ti and its alloys used in implants and AM of them, osseointegration. This paper has presented a conceptual understanding and AM process of implants from design to manufacture with some reports of current and important instances. Since suitable combinations for biomaterials, AM technique, secondary process, as well as biological analyses are critical in implants, in-vivo, and vitro studies should be increased to improve implant performance and achieve satisfactory quality. However, AM has been preferred in implant fabrication due to various advantages, researches should be intensified on decreasing high setup and raw material costs, secondary treatment; increasing fabrication a, implant lifespan, and stability; topology optimization topics. Ti-based biomaterials can also be coated using different processes of deposition.

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